REMARKS

The Office Action dated December 26, 2002 addressed claims 1, 5 and 63-104, with claims 101-104 being withdrawn from consideration, and claims 73-75 and 92-98 being in position for allowance provided they are rewritten in independent form. In response to the Office Action, claims 101-104 have been cancelled without prejudice. However, no other amendments have been made at the present time because the Applicants respectfully disagree with the rejections under 35 U.S.C. § 103(a) as set forth in the arguments below. However, the spelling of paclitaxel at page 46, line 21 has been corrected, as requested by the Examiner.

Rejection Under 35 U.S.C. § 103 based on Zhang and Hunter

Claims 1, 5, 63-72, 76-91 and 99-100 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Zhang et al. ("Zhang") in view of Hunter et al. ("Hunter"). Before proceeding to discuss the rejection, Applicants would like to clarify that Zhang et al. refers to Zhang, X. et al., *International Journal of Pharmaceutics* 137:199-208, 1996 (rather than, *e.g.*, Zhang, X. et a., *Anticancer Drugs* 8(7):696-701, 1997, as set forth as entry A7 on Applicants' PTO-1449 (modified) form filed with the Fourth Supplemental Information Disclosure Statement of September 18, 2002). Hunter et al. refers to U.S. Patent 5,994,341.

The Office Action takes the position that Zhang teaches a paste comprising a triblock copolymer and paclitaxel, and that Hunter teaches to dissolve paclitaxel in MePEG prior to mixing with a polymer. Based on these disclosures, the Office Action draws the conclusion that it would have been obvious to add MePEG to the compositions of Zhang to achieve the beneficial effects of pre-dissolving paclitaxel as disclosed by Hunter. This rejection is respectfully but strenuously traversed for the following reasons.

Applicants have previously argued, and continue to assert, that the combination of Zhang and Hunter would not motivate one of ordinary skill in the art to prepare Applicants' invention. However, for the sake of argument, even assuming one of ordinary skill in the art were to proceed as the Examiner is suggesting, and that the Examiner's burden of supporting a *prima facie* case of obviousness has been met under 35 U.S.C. § 103, one needs to ask "what would the ordinarily skilled artisan expect to form?" As discussed below, the combination of

materials as recited in Applicants' claims provides a composition having very surprising performance properties, and based on the evidence of non-obvious results as discussed below and described in Applicants' specification, Applicants respectfully contend that they have overcome this rejection (even assuming it is appropriate). Applicants' position is explained below.

Both Zhang and the cited portion of Hunter are directed to thermopastes. A thermopaste is a solid composition having a low melting point. The idea behind thermopastes is that a thermopaste can be heated to a molten form, then injected into a patient whereupon the thermopaste spontaneously cools to the internal temperature of the host, about 37°C, and at this relatively low temperature returns to a solid form. The thermopaste within the patient serves as a reservoir or depot for the drug, where the drug is gradually released into the vicinity of the thermopaste. Thus, a thermopaste is a composition that is a solid at the internal temperature of the host (ca. 37°C) but is molten at some higher temperature.

We know that Zhang is directed to thermopastes based on many comments made throughout Zhang. For instance, the Abstract at page 199 (see lines 9-10) states that the pastes of Zhang harden at 37°C. At page 200, left column, first full paragraph, Zhang indicates that delivery of a paste to a subject needs to be preceeded by warming of the paste. Page 201, left column, last paragraph, indicates that cylinders may be formed by extruding the molten paste; cylinders could not logically be formed from a liquid composition. Accordingly, Zhang is directed to thermopaste compositions.

Hunter also writes about thermopaste, and the portion of Hunter cited by the Examiner is directed to making and evaluating thermopastes. Consistent with Applicants discussion above, Hunter describes a thermopaste generally at col. 17, lines 58-67, where it is stated that a thermopaste refers to a composition that is liquid at one temperature and solid or semi-solid at another temperature. Thermopaste is further discussed by Hunter at col. 49, lines 2-5 and 19-56, where it is explained that a thermopaste is molten at a high temperature, *e.g.*, 60°C, but is solid or semi-solid at a lower temperature, *e.g.*, body temperature of ca. 37°C.

To support the rejection, the Examiner has cited col. 60, lines 13-16, 40-41 and col. 61, lines 12-13, all of which are within Example 14 of Hunter. Hunter refers to the

compositions of Example 14 variously as pastes or thermopastes, but it is clear that the compositions of Example 14 are solid at room temperature. See, *e.g.*, col. 60, lines 30-34, which discuss the melting points of the pastes (see Figure 18A (Sheet 25 of 75) where the melting points range from ca. 48.5°C to ca. 43.5°C); col. 60, lines 44-55, which discuss the brittleness of the compositions (liquids cannot be brittle, only solids can be brittle); col. 61, lines 1-8, which specifically refers to the materials of Example 14 as "thermopastes" and writes in terms of "pellets"; col. 61, lines 9-22, which again specifically refers to the compositions of Example 14 as thermopastes; and col. 61, lines 24-36, which addresses the strength analysis of various compositions as measured on solid polymer tablets. Thus, it can be seen that the portion of Hunter relied upon by the Examiner is specifically addressed to "thermopastes".

For completeness, it is noted that Hunter also discusses pastes containing a homopolymer (PCL, *i.e.*, polycaprolactone) and a liquid water-soluble polymer (MePEG, *i.e.*, methoxy terminated polyethylene glycol) in Example 34 at col. 80, lines 29-67. Once again, however, these pastes are disclosed by Hunter as thermopastes. This can be seen by reference to col. 80, lines 45-51, which references Figure 44A (see Sheet 57 of 75) as disclosing melting points for the pastes, where those melting points range from ca. 48.5°C to ca. 43.5°C. See also col. 80, lines 52-55, which discusses the tensile strength of the compositions, where tensile properties may only be measured on solids.

Thus, Zhang exclusively, and Hunter in relevant part, are both directed to thermopastes. However, Applicants' claimed invention is not a thermopaste. Applicants have made the remarkable discovery that a composition that is a liquid at room temperature can be delivered to a subject, whereupon the liquid solidifies into a drug-releasing body. Applicants' invention overcomes a shortcoming of thermopastes, namely, that one needs to heat a thermopaste to a temperature above body temperature in order to create a fluid form of the composition, and then deliver this molten form to the subject whereupon cooling occurs and the fluid becomes a solid. This heating process is not particularly convenient from a practical point of view. Applicants have very surprisingly discovered a composition that can be delivered as a fluid at about room temperature and yet will form a solid body in vivo.

As explained in Applicants' specification, this remarkable phenomenon is believed to occur because when the composition is injected into a host, the water-soluble polymer component (or at least a portion of this component that is near the exterior surface of the injected composition) disperses away from the block copolymer and drug, thereby raising the melting point of the composition so that it becomes a solid at body temperature. Accordingly, Applicants' claimed composition comprises a block copolymer of hydrophobic and hydrophilic blocks in combination with a water-soluble polymer that presumably interacts with the hydrophilic component of the block copolymer resulting in solubilization of the block copolymer. The water soluble polymer separates from the block copolymer after the composition has been delivered to the patient. Since the drug is hydrophobic, it is retained in the (now solid) block copolymer, and is gradually released into the patient.

Whether Applicants' theory regarding the mechanism of action of Applicants' composition is correct or not, the fact remains that Applicants have developed and are claiming a composition that is fluid at room temperature. This is in sharp contrast to the compositions of Zhang and Hunter in relevant part, both of which are directed to thermopastes.

As acknowledged by the Examiner, neither Zhang nor Hunter prepare compositions accordingly to Applicants' claimed invention. That is, neither Zhang nor Hunter disclose a composition that contains both a biodegradable water soluble block copolymer that is a solid or wax at 37°C (comprising both hydrophilic and hydrophobic blocks), and a biodegradable water soluble polymer that is a liquid at 25°C. The Office Action has taken the position, however, that it would be obvious to add MePEG (as used in the Hunter thermopastes) to the thermopaste compositions of Zhang (which contain a hydrophobic drug and a block copolymer) in order to arrive at Applicants claimed invention. However, it is respectfully submitted that this extrapolation from Zhang and Hunter would, if performed, be expected to result in a thermopaste. That is, combining thermopaste-forming materials from Hunter and thermopaste-forming materials from Zhang would be expected, logically, to lead to a thermopaste. However, as explained above, Applicants have very surprisingly found that this particular combination does not lead to a thermopaste, but instead leads to a composition that is

fluid at room temperature, yet still forms a solid mass when placed *in vivo*. Such a result is nonobvious and surprising based on the combined disclosures of Zhang and Hunter.

Specific details about representative compositions of the present invention are set forth in the Examples. See, *e.g.,* Example 5 at page 50, line 7 to page 53, line 10 (and particularly, *e.g.,* page 52, lines 9-16, where "TB" stands for triblock copolymer, and MePEG350 stands for methoxy polyethylene glycol having a molecular weight of 350) which indicates that the compositions of Applicants' invention are liquids at room temperature; and Example 7 at page 56, line 1 to page 57, line 7 (and particularly, *e.g.,* page 56, lines 13-22, demonstrating that the liquid compositions solidify in the presence of water, so long as a hydrophobic drug is present in the composition).

In view of the foregoing comments, Applicants respectfully contend that even if a rejection under 35 U.S.C. § 103 is appropriate, Applicants have demonstrated surprising results that overcome the rejection. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Rejection Under 35 U.S.C. § 103 based on Youxin and Hunter

The disclosure of Youxin (J. Controlled Release, 32:121-128, 1994) is directed exclusively to the delivery of hydrophilic proteins, and more specifically is directed to the delivery of bovine serum albumin (BSA). See, *e.g.,* page 122, left column, first full paragraph (regarding delivering hydrophilic proteins); page 122, right column, final paragraph (BSA was dissolved in water at 0.3g/ml); page 126, right column, first paragraph (water-soluble drugs such as peptides and proteins); page 126, right column, last sentence (controlled release of hydrophilic model protein); and page 127, left column, second paragraph (hydrophilic drug substances). In contrast, Applicants claimed invention is directed to hydrophobic drugs. It is well known in the art that methods for delivering hydrophilic drugs are not generally utilized for delivering hydrophobic drugs, and *vice versa.* Certainly Youxin does not teach or suggest that both hydrophobic and hydrophilic drugs can be delivered by the method of Youxin. Accordingly, Applicants respectfully contend that one of ordinary skill in the art would not refer to Youxin for providing teaching that is relevant to the subject matter of Applicants' invention, namely, the

delivery of hydrophobic drugs. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection Under 35 U.S.C. § 103 based on Cha and Hunter

The disclosure of Cha (U.S. Patent 5,702,717) is directed to compositions of block copolymers having reverse thermal gelation properties (see, *e.g.*, col. 7, line 66 to col. 8, line 1). That is, they are liquids at room temperature (ca. 23°C) but form gels at body temperature (ca. 37°C). These special block copolymers are prepared when the hydrophilic block makes up about 50-85% of the copolymer and the hydrophobic block makes up about 15-50% by weight of the copolymer (see, *e.g.*, col. 8, lines 30-35 and col. 12, lines 53-58). In contrast, the block copolymers of Applicants' claimed invention have a preponderance of hydrophobic blocks (see, *e.g.*, claim 1, which recites that the block copolymer comprises greater than 50% hydrophobic blocks). Accordingly, Applicants are not claiming the use of the same block copolymers as disclosed by Cha.

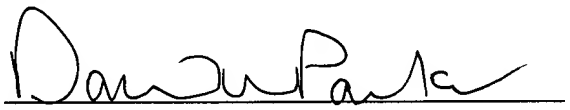
As for combining Cha with Hunter, Applicants note that the relevant portions of Hunter are directed to thermopastes (compositions that are heated to above body temperature to achieve a fluid state, and then allowed to cool to body temperature whereupon they adopt a solid state), while Cha is directed to compositions having reverse gelation properties (compositions that are fluid at room temperature but gel/solidity when they are warmed to body temperature). In other words, Cha and Hunter take diametrically opposed approaches to drug delivery. Accordingly, Applicants respectfully contend that one of ordinary skill in the art would not be motivated to combine components from the thermopastes of Hunter and components from the compositions of Cha. Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the foregoing remarks Applicants respectfully contend that the pending claims are patentable in view of Zhang, Hunter, Cha, Youxin and combinations thereof. Accordingly, a Notice of Allowance for the application is earnestly solicited.

The Commissioner is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC



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